# Comparison with randomized controlled trials as a strategy for evaluating instruments in Mendelian randomization

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The Mendelian randomization (MR) approach uses genetic variants as instrumental variables to study the effect of an exposure on an outcome (1). In this way, by selecting genetic variants that serve as instrumental variables for drug effects, it can also be possible to study corresponding drug side-effects and repurposing potential (2). Such an approach has recently been applied to antihypertensive drugs, by two separate research groups independently of each other (3, 4). Here, the authors of these two papers collaboratively discuss an approach that can be used for validating instruments for such study.

Both of the discussed research papers studied antihypertensive drugs using genetic variants located at the locus of the gene corresponding to their respective protein targets. The work by Gill *et al*. selected instruments for antihypertensive drug classes as genetic variants at the corresponding protein target's gene, promotor or enhancer region that were also associated with systolic blood pressure (SBP) at genome-wide significance ($P<5x10^{-8}$) (3). In contrast, Walker *et al*. selected instruments as genetic variants at the corresponding protein target's gene that were marked as the 'best SNP' for relation to expression of that gene in any tissue within the Genotype-Tissue Expression (GTEx) project data (5). These genetic variants were then retained for the main analysis, regardless of the tissue that they were identified in, if there was evidence that they also had an effect on SBP in two-sample MR (4).

Randomized controlled trials (RCTs) represent the gold-standard for investigating drug effects, and although they can be limited by time and resource requirements, they continue to be regarded as the definitive study design for guiding clinical practice (6). Where RCT data are available on drug effects, these can be used to explore the validity of instruments selected to study the corresponding drug in MR analyses (3). When using such a strategy, it is however important to appreciate that MR and RCTs are intrinsically different approaches, and therefore the estimates that they generate are not equivalent or interchangeable. Given that MR measures the lifelong cumulative effect of genetic predisposition, it follows that its estimates may be greater than those obtained from clinical

intervention at a discrete time point, such as in a RCT. Similarly, the population characteristics for those considered within an MR and RCT setting may not coincide. Other potential dangers of such comparison include the scenario where the MR estimates are biased due to incorporation of pleiotropic variants. Of note, bias in MR related to pleiotropy can also vary depending on the particular exposure-outcome pair under study – variants that effect one outcome through effects independent of the exposure may not necessarily do so for another. Despite these limitations, where MR analysis is being performed to investigate the clinical effects of a drug, it should generally follow that their findings are at least in-keeping with those obtained in corresponding RCTs.

In the paper by Walker *et al*., genetic instruments for antihypertensive drug classes were identified to explore their potential for repurposing in the prevention of Alzheimer's disease (4). For the angiotensin-converting enzyme (ACE) inhibitor, beta-adrenoceptor blocker, calcium channel blocker and thiazide-like diuretic drug classes, corresponding RCT meta-analysis estimates are available for their effect (against placebo) on risk of coronary heart disease (CHD) and stroke (7). We can compare MR estimates with corresponding RCT meta-analysis results by using the genetic instruments that Walker *et al*. identified for each drug classes (4), and performing two-sample inverse-variance weighted (or ratio method where only a single instrument variant is available) MR analyses for risk of CHD and stroke respectively (7). Here, we do this using publicly available genome-wide association study summary data on 60,801 CHD cases and 123,504 controls (multi-ethnic) (8), and 40,585 stroke cases and 406,111 controls (European ancestry) (9). MR estimates are scaled to the effect on SBP observed in RCT meta-analyses for the respective drug class (21.1 mmHg decrease for ACE inhibitors, 9.5 mmHg decrease for beta-adrenoceptor blockers, 8.9 mmHg decrease for calcium channel blockers, and 12.6mmHg decrease for thiazide-like diuretics) (7) to allow comparison with RCT results, with the further assumption that odds ratio estimates approximate to relative risk estimates for CHD and stroke (3). The MR and RCT estimates are compared in Figure 1, and their concordance supports that the instruments incorporated for MR are valid.

Previous RCTs investigating the effect of treatment with antihypertensive medications have focused on dementia generally, rather than specifically considering Alzheimer's disease (10, 11). Furthermore, these trials studied combinations of antihypertensive medication classes. While both the RCTs and the MR analyses performed by Walker *et al*. have focused on clinically diagnosed cases, thus introducing the possibility of misclassification, the different exposure and outcome definitions still preclude direct comparison of their results from being used to explore MR instrument validity.

To summarize, evidence from RCTs provides gold-standard evidence which can be used to validate putative genetic proxies for specific drug targets. Although there are limitations to such an approach, any discordance between RCT and MR findings could be used to highlight the inclusion of invalid instruments.

## Data availability

The code and data used to perform the analyses presented in this article are provided on GitHub: https://github.com/venexia/rct-instrument-comparison.


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## Conflict of interest

Dr Walker is currently working on a manuscript in collaboration with GlaxoSmithKline plc that explores whether Mendelian randomization can predict drug success, but she does not receive financial support from the company. Dr Davies has worked on unrelated projects funded as part of the Global Research Awards for Nicotine Dependence, which is an independent grant giving body funded by Pfizer. The remaining authors have no conflicts of interest to declare.

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**Figure legend**

Figure 1. Mendelian randomization estimates of antihypertensive drug effects on coronary heart disease and stroke risk, as compared to results from randomized controlled trial meta-analyses. The 95% confidence intervals are provided in brackets and a $\log_{10}$ scale is used.